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Platelet Function During Extended Prasugrel and Clopidogrel Therapy for Patients With ACS Treated Without Revascularization

The TRILOGY ACS Platelet Function Substudy

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Context The relationship of platelet function testing measurements with outcomes in patients with acute coronary syndromes (ACS) initially managed medically without revascularization is unknown.

Objective To characterize the differences and evaluate clinical outcomes associated with platelet reactivity among patients with ACS treated with clopidogrel or prasugrel.

Design, Setting, and Patients Patients with medically managed unstable angina or non–ST-segment elevation myocardial infarction were enrolled in the TRILOGY ACS trial (2008 to 2011) comparing clopidogrel vs prasugrel. Of 9326 participants, 27.5% were included in a platelet function substudy: 1286 treated with prasugrel and 1278 treated with clopidogrel.

Interventions Aspirin with either prasugrel (10 or 5 mg/d) or clopidogrel (75 mg/d); those 75 years or older and younger than 75 years but who weighed less than 60 kg received a 5-mg prasugrel maintenance dose.

Main Outcome Measures Platelet reactivity, measured in $P2Y_{12}$ reaction units (PRUs), was performed at baseline, at 2 hours, and at 1, 3, 6, 12, 18, 24, and 30 months after randomization. The primary efficacy end point was a composite of cardiovascular death, myocardial infarction, or stroke through 30 months.

Results Among participants younger than 75 years and weighing 60 kg or more, the median PRU values at 30 days were 64 (interquartile range [IQR], 33-128) in the prasugrel group vs 200 (IQR, 141-260) in the clopidogrel group ($P<.001$), a difference that persisted through all subsequent time points. For participants younger than 75 years and weighing less than 60 kg, the median 30-day PRU values were 139 (IQR, 86-203) for the prasugrel group vs 209 (IQR, 148-283) for the clopidogrel group ($P<.001$), and for participants 75 years or older, the median PRU values were 164 (IQR, 105-216) for the prasugrel group vs 222 (IQR, 148-268) for the clopidogrel group ($P<.001$). At 30 months the rate of the primary efficacy end point was 17.2% (160 events) in the prasugrel group vs 18.9% (180 events) in the clopidogrel group ($P=.29$). There were no significant differences in the continuous distributions of 30-day PRU values for participants with a primary efficacy end point event after 30 days (n=214) compared with participants without an event (n=1794; $P=.07$) and no significant relationship between the occurence of the primary efficacy end point and continuous PRU values (adjusted hazard ratio [HR] for increase of 60 PRUs, 1.03; 95% CI, 0.96-1.11; $P=.44$). Similar findings were observed with 30-day PRU cut points used to define high on-treatment platelet reactivity—PRU more than 208 (adjusted HR, 1.16; 95% CI, 0.89-1.52, $P=.28$) and PRU more than 230 (adjusted HR, 1.20; 95% CI, 0.90-1.61; $P=.21$).

Conclusions Among patients with ACS without ST-segment elevation and initially managed without revascularization, prasugrel was associated with lower platelet reactivity than clopidogrel, irrespective of age, weight, and dose. Among those in the platelet substudy, no significant differences existed between prasugrel vs clopidogrel in the occurence of the primary efficacy end point through 30 months and no significant association existed between platelet reactivity and occurrence of ischemic outcomes.

Trial Registration clinicaltrials.gov Identifier: NCT00699998

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PLATELET-RICH THROMBUS FORmation plays a major role in the occurrence of ischemic events in patients with acute coronary syndromes (ACS).[1] A large body of evidence, primarily based on single ex vivo measurements, demonstrates an association between high on-treatment platelet reactivity to adenosine diphosphate and the occurrence of ischemic events among patients treated with clopidogrel following percutaneous coronary intervention (PCI); however, many questions regarding this association remain unanswered.[2-4]

For editorial comment see p 1806.

First, few studies have included longitudinal assessments of platelet function to evaluate time-dependent relationships

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with platelet reactivity and ischemic event occurrence.[5,6] Second, a long-term serial comparison of platelet reactivity during clopidogrel treatment vs newer, more potent $P2Y_{12}$ inhibitor therapies has not been undertaken. Third, a large platelet function substudy has never been embedded within a large clinical trial of antiplatelet therapy.[3] Fourth, there is no information available regarding the association between platelet function measurements and the occurrence of ischemic events in elderly patients with ACS, and in patients with ACS whose condition is managed medically without revascularization.[3]

We therefore conducted a large serial platelet function substudy within the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial, a randomized, double-blind, active-control, event-driven trial comparing prasugrel vs clopidogrel therapy in patients with unstable angina or non–ST-segment elevation myocardial infarction (UA/NSTEMI) who were managed medically without planned revascularization.[7] Comparable clinical outcomes were observed between treatment groups in the overall trial, with a late separation of event curves seen after 12 months. Both agents are thienopyridine $P2Y_{12}$ inhibitors that attenuate platelet response to adenosine diphosphate; prasugrel has been shown to be more potent and to have less variable platelet inhibition than clopidogrel.[8]

The objectives of our study were to characterize differences in platelet reactivity between treatment groups over time, to delineate the relationship of platelet reactivity with ischemic end point occurrence, and to determine a threshold for high platelet reactivity that optimizes the ability to discriminate between patients with and without ischemic event occurrence.

METHODS

Main Study Protocol and Treatment

The eligibility criteria, design, and results of the TRILOGY ACS study have been reported.[7] In the overall trial, 9326 patients with UA/NSTEMI at 966 sites in 52 countries were enrolled from 2008 to 2011. Participants were randomly assigned to receive either prasugrel or clopidogrel therapy in a double-blind, double-dummy fashion as previously described. The daily prasugrel maintenance dose was 10 mg in study participants younger than 75 years who weighed 60 kg or more and 5 mg for all participants aged 75 years or older and younger than 75 years and with a body weight less than 60 kg. The daily clopidogrel maintenance dose was 75 mg for all participants. Concomitant daily treatment with aspirin was required and low-dose aspirin was strongly recommended. Treatment duration was between 6 and 30 months.

Platelet Function Substudy Protocol

Of the 52 countries that participated in the trial, 25 were selected to enroll in the platelet function substudy (eTable 1). Countries were selected across the regions represented in the trial to provide geographic balance, but no specific criteria were used to select individual countries. The TRILOGY ACS study and the embedded platelet function substudy were approved by each site's institutional review board and ethics board, and all participants provided written informed consent. Sites participating in the substudy were instructed to enroll all consenting participants who were randomized into the main trial into the substudy.

Each participating site was also provided with 2 encrypted VerifyNow devices (Accumetrics Inc). VerifyNow $P2Y_{12}$ is a whole-blood, turbidimetric-based assay that measures platelet agglutination to fibrinogen-coated polystyrene beads in response to adenosine diphosphate. Assay results, expressed as $P2Y_{12}$ reaction units (PRUs)[5] were encrypted at the site for double-blinding. Blood samples were collected at baseline, at 2 hours, and at 1, 3, 6, 12, 18, 24, and 30 months after randomization. Sites were instructed to collect samples only during the interval when participants were taking the blinded study drug.

Participants with at least 1 valid PRU measurement were included in the analysis. Submitted PRU values were excluded if the assay was performed within 7 days of glycoprotein IIb/IIIa inhibitor therapy or less than 10 minutes or more than 4 hours after sample collection via venipuncture; if the device-reported percent inhibition was more than 100%; or if the baseline or PRU value was more than 500 or the baseline was less than 100.

End Points

The outcome measurement for platelet function was the PRU value. The primary efficacy end point for both the TRILOGY ACS trial and this substudy was the composite of cardiovascular death, myocardial infarction (MI), and stroke through 30 months.[7] Key secondary end points chosen for analysis were all-cause death and the component end point of all MI events because these end points have been previously analyzed with platelet function testing in patients undergoing PCI and because we also wanted to account for all deaths in the analysis.[2-4]

Statistical Analysis

Baseline characteristics were compared between the platelet function substudy and nonsubstudy cohorts and by treatment within the substudy cohort. Continuous variables are presented as medians (interquartile ranges [IQR]), and differences were compared using the analysis of variance *F* test when the assumption of normality was satisfied; otherwise, the Kruskal-Wallis test was used. Categorical variables are presented as counts (proportions). Differences were compared using the χ^2 test when cell frequencies were sufficient; otherwise, an exact test was used. Event counts and unadjusted Kaplan-Meier rates at 30 months after randomization were presented for the same groups and compared using the log-rank test. We did not perform formal sample-size power calculations because ischemic event rates and the relationship of platelet function to ischemic events in this population were unknown before the TRILOGY ACS was conducted, and the number of patients expected to be enrolled at the participating sites could not be ascer-

tained when the present substudy was planned.

To determine the relationship of continuous PRU values with the risk of an ischemic event, a Cox model regressing time to first event on PRU was fit with 3 separate approaches. The 3 ischemic outcomes modeled were the primary efficacy end point, all-cause death, and all MI events. Variables included in the modeling process included those derived from the Global Registry of Acute Coronary Events (GRACE) mortality risk models as well as variables unique to the trial.[8] All variables were included in the models collectively, without a formal selection process. First, PRU was treated as time-varying covariate in which the most recent PRU value measured was used when estimating the relationship of PRU at each fail-time during the study period. To account for events that occurred between 5 and 30 days after randomization, we assumed the 30-day PRU value represented steady-state treatment and used it as the PRU value at these failure times. For events between randomization and 5 days, we used the 2-hour PRU value as the PRU value at these failure times.

Second, to determine whether PRU values measured 30 days after randomization predicted risk, we fit a Cox model landmarked at 30 days regressing time to first event on PRU. The 30-day PRU measurement was treated as a baseline variable, and participants with events occurring before 30 days were excluded from the analysis.

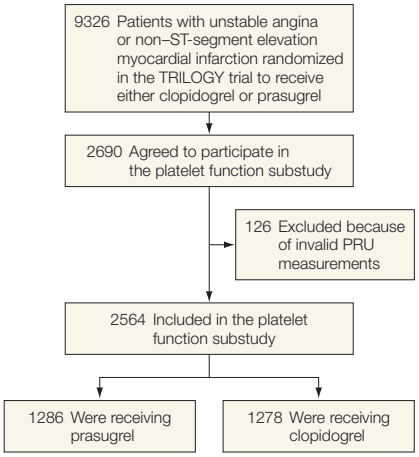
Third, multiple imputation techniques were used with both modeling procedures to account for potential bias induced by missing PRU values at all time points except for month 30, which was not a prespecified time point and happened to coincide with the last study visit for some participants, and for missing values in adjustment variables. Both adjusted and unadjusted analyses were performed for each model and the relationship of continuous PRU values with the outcome studied was modeled as a 60-unit PRU increase.[9]

To evaluate the relationship of dichotomous determinations of high platelet reactivity on risk of an event, a Cox model regressing time to first event on high platelet reactivity status was fit. *High platelet reactivity status* was defined as having a PRU value higher than a predetermined cut point derived from prior studies involving patients who had undergone PCI (on-treatment PRU >208 and >230).[2] In addition, the high platelet reactivity cut point based on receiver operating characteristic (ROC) curve analysis of continuous 30-day PRU data (>178 PRU) with the primary efficacy end point was also evaluated (the maximum of the product of sensitivity and specificity was determined from this data set; eFigure 1 available at http://www.jama.com).

Kaplan-Meier event rates for the primary efficacy end point, all-cause death, and all MI events starting at the 30-day landmark period through 30 months were compared among participants with and without high platelet reactivity using the more than 208 and more than 230 PRU cut points. Furthermore, participants with vs without a primary efficacy end point event after 30 days were compared with a continuous distribution of 30-day PRU values using a Wilcoxon rank-sum test (nonparametric). To determine whether high platelet reactivity status at 30 days after randomization was predictive of the end points analyzed, a Cox model landmarked at 30 days regressing time to first event on high platelet reactivity status was fit. The 30-day PRU measurement was used to determine high platelet reactivity status, which was treated as a baseline variable; participants with events occurring before 30 days were excluded from the analysis. Both adjusted and unadjusted analyses were performed for the aforementioned ischemic outcomes.

All statistical tests were performed at a significance level of .05. All analyses were performed by independent statisticians (B.N. and M.N.) at the Duke Clinical Research Institute, Durham, North Carolina using SAS 9.3 and R 2.14.1 (SAS Institute Inc).

Figure 1. Flow Diagram of the Platelet Function Substudy



PRU indicates $P2Y_{12}$ reaction unit.

RESULTS

Study Participants

Among 9326 participants enrolled in TRILOGY ACS, 2690 (28%) were initially enrolled in the platelet function substudy. After database lock, it was determined that 126 did not have a valid PRU measurement, leaving a total of 2564 participants (27.5% of the total population) whose data were included in the analysis (FIGURE 1). Approximately 20% of the substudy participants were 75 years or older (n=515) and approximately 16% (n=399) weighed less than 60 kg (TABLE 1). Compared with those not included, participants in the substudy analyses were less likely to be 75 years or older, to have NSTEMI on presentation, and to have prior peripheral arterial disease and prior coronary artery bypass graft surgery, but they were more likely to have prior heart failure and to be treated with a daily aspirin dose of less than 100 mg. Among participants in the platelet function substudy, baseline characteristics were well balanced between treatment groups.

Platelet Function Measurements and Treatment

The number of valid platelet function measurements decreased sequentially at each prespecified time point based on the in-

herent variable duration of follow-up in the study for each participant (eTable 2 available at http://www.jama.com). Baseline median PRU values were similar between both treatment groups (FIGURE 2), reflecting treatment with open-label clopidogrel for the index ACS event before randomization in more than 95% of participants (Table 1).

Table 1. Baseline Characteristics of TRILOGY ACS Platelet Function Substudy Participants

	No./Total (%) of Patients in Baseline Study			No./Total (%) of Patients in Substudy Treatment Groups		
	Included in Substudy (n = 2564)	Not Included in Substudy (n = 6762)	*P* Value	Prasugrel (n = 1286)	Clopidogrel (n = 1278)	*P* Value
Age, y						
≥75	515/2564 (20.1)	1568/6762 (23.2)	.001	244/1286 (19.0)	271/1278 (21.2)	.16
<75	2049/2564 (79.9)	5194/6762 (76.8)		1042/1286 (81.0)	1007/1278 (78.8)	
Women	1002/2564 (39.1)	2648/6762 (39.2)	.94	492/1286 (38.3)	510/1278 (39.9)	.39
Weight, kg						
<60	399/2564 (15.6)	1002/6755 (14.8)	.38	199/1286 (15.5)	200/1278 (15.6)	.90
≥60	2165/2564 (84.4)	5753/6755 (85.2)		1087/1286 (84.5)	1078/1278 (84.4)	
Disease classification						
Unstable angina	843/2564 (32.9)	1963/6762 (29.0)	<.001	429/1286 (33.4)	414/1278 (32.4)	.60
NSTEMI	1721/2564 (67.1)	4799/6762 (71.0)		857/1286 (66.6)	864/1278 (67.6)	
Killip class II-III	310/2563 (12.1)	825/6755 (12.2)	.88	152/1285 (11.8)	158/1278 (12.4)	.68
Time to treatment, median (IQR), h[a]	107.9 (61.0-160.0)	108.1 (62.9-159.5)	.57	103.0 (58.7-159.6)	110.6 (62.8-160.0)	.31
Medical history						
Family history of CAD	713/2291 (31.1)	1805/5990 (30.1)	.38	353/1147 (30.8)	360/1144 (31.5)	.72
Hypertension	2102/2557 (82.2)	5523/6746 (81.9)	.71	1061/1280 (82.9)	1041/1277 (81.5)	.37
Hyperlipidemia	1392/2364 (58.9)	3855/6506 (59.3)	.75	685/1170 (58.5)	707/1194 (59.2)	.74
Diabetes mellitus	947/2561 (37.0)	2592/6745 (38.4)	.20	460/1285 (35.8)	487/1276 (38.2)	.21
Current or recent smoking	498/2534 (19.7)	1346/6694 (20.1)	.63	246/1267 (19.4)	252/1267 (19.9)	.76
Prior						
Myocardial infarction	1110/2549 (43.5)	2877/6697 (43.0)	.61	565/1279 (44.2)	545/1270 (42.9)	.52
PCI	665/2555 (26.0)	1760/6715 (26.2)	.86	333/1282 (26.0)	332/1273 (26.1)	.95
CABG surgery	357/2561 (13.9)	1097/6742 (16.3)	.006	173/1284 (13.5)	184/1277 (14.4)	.49
Peripheral arterial disease	140/2515 (5.6)	540/6640 (8.1)	<.001	63/1262 (5.0)	77/1253 (6.1)	.21
Atrial fibrillation	218/2513 (8.7)	492/6588 (7.5)	.06	109/1265 (8.6)	109/1248 (8.7)	.92
Heart failure	508/2538 (20.0)	1121/6727 (16.7)	<.001	251/1271 (19.7)	257/1267 (20.3)	.74
Baseline risk assessment						
GRACE risk score, median (IQR)[b]	122.0 (105.0-140.0)	121.0 (105.0-139.0)	.81	120.0 (104.0-139.0)	122.0 (106.0-140.0)	.11
Values (range)	(42-201)	(56-205)		(42-205)	(41-210)	
Creatinine clearance, median (IQR), mL/min	74.0 (55.3-97.0)	72.3 (53.4-95.8)	.13	74.1 (55.2-97.4)	74.0 (55.6-96.1)	.61
Prerandomization treatment						
Clopidogrel stratum						
No prerandomization clopidogrel	121/2564 (4.7)	277/6761 (4.1)	.02	59/1286 (4.6)	62/1278 (4.9)	.79
Clopidogrel started in hospital and continued until randomization	1736/2564 (67.7)	4777/6761 (70.7)		865/1286 (67.3)	871/1278 (68.2)	
Home clopidogrel continued until randomization	707/2564 (27.6)	1707/6761 (25.2)		362/1286 (28.1)	345/1278 (27.0)	
Duration of clopidogrel before treatment start, median (IQR), h	108.0 (64.5-153.5)	107.0 (64.0-155.3)	.99	108.2 (64.3-156.8)	108.0 (64.5-150.6)	.93
Angiography prior to randomization	993/2564 (38.7)	2858/6761 (42.3)	.002	492/1286 (38.3)	501/1278 (39.2)	.62
Concomitant medication[c]						
Aspirin, daily dose, mg						
<100	1022/2564 (39.9)	2087/6762 (30.9)	<.001	516/1286 (40.1)	506/1278 (39.6)	.78
100-250	1166/2564 (45.5)	3790/6762 (56.0)	<.001	592/1286 (46.0)	574/1278 (44.9)	.57
>250	187/2564 (7.3)	486/6762 (7.2)	.86	87/1286 (6.8)	100/1278 (7.8)	.30
β-Blocker	1966/2564 (76.7)	5285/6762 (78.2)	.13	1002/1286 (77.9)	964/1278 (75.4)	.14
ACE-I/ARB	1853/2564 (72.3)	5174/6762 (76.5)	<.001	912/1286 (70.9)	941/1278 (73.6)	.13
Statin	2107/2564 (82.2)	5669/6762 (83.8)	.06	1058/1286 (82.3)	1049/1278 (82.1)	.90
Proton-pump inhibitor	608/2564 (23.7)	1736/6762 (25.7)	.05	303/1286 (23.6)	305/1278 (23.9)	.86

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndromes; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass graft; CAD, coronary atherosclerotic disease; GRACE, Global Registry of Acute Coronary Events; IQR, interquartile range; NSTEMI, non–ST-segment elevation myocardial infarction; PCI percutaneous coronary intervention.

Conversion factor: To convert creatinine clearance from mL/min/1.73 m^2 to mL/s/m^2, multiply by 0.0167.

[a] Measured from time of first medical contact.

[b] Higher GRACE risk scores are associated with a higher predicted risk of 6-mo mortality.[8]

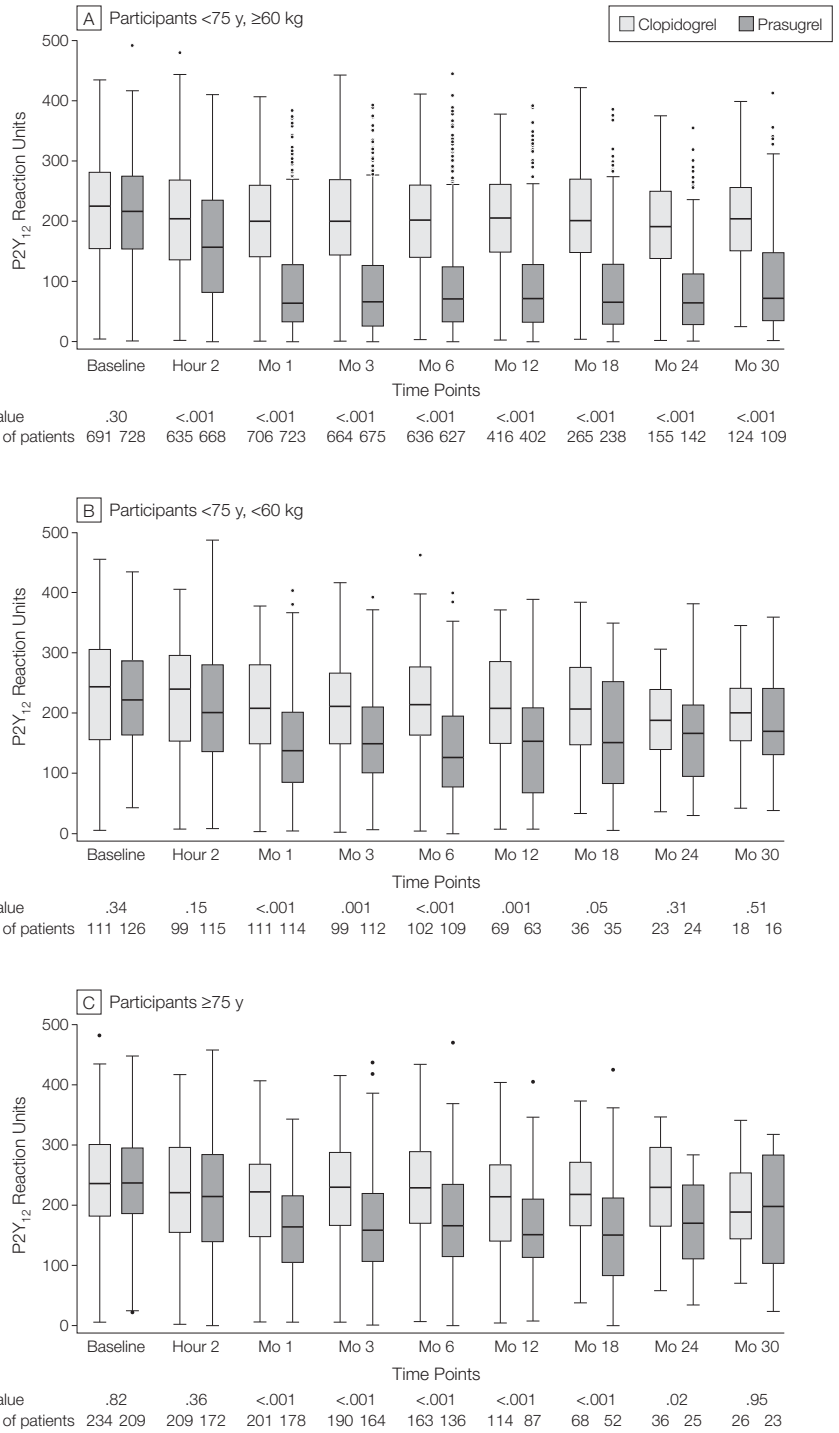
[c] Assessed at time of randomization.

After randomization, prasugrel treatment was associated with lower median PRU values than clopidogrel treatment starting at 2 hours after the first dose of the study drug, with pronounced differences at all time points from 30 days through 30 months in the subgroup of participants younger than 75 years and weighing 60 kg or more (all of whom received prasugrel 10 mg/d; Figure 2A). Within this group, median 30-day PRU values were 64 (interquartile range [IQR], 33-128) for the prasugrel group vs 200 (IQR, 141-260) for the clopidogrel group ($P<.001$). Among participants younger than 75 years and weighing less than 60 kg and those 75 years or older who received the 5-mg/d maintenance dose of prasugrel, significant differences in median PRU values through 18 months were observed compared with those treated with clopidogrel, but these differences were less pronounced than for participants who received prasugrel 10 mg/d (Figure 2B and C).

At 30 days, 5-mg prasugrel was associated with a lower 30-day PRU response than was clopidogrel for participants younger than 75 years who weighed less than 60 kg with a median of 139 (IQR, 86-203) vs 209 (IQR, 148-283; $P<.001$) and participants 75 years or older had a median PRU of 164 (IQR, 105-216) vs 222 (IQR, 148-268) in the clopidogrel group; $P<.001$). The 30-day median PRU values for participants treated with the 10-mg prasugrel dose were significantly lower than those observed with the 5-mg prasugrel dose for participants younger than 75 years and weighing less than 60 kg and for participants aged 75 years or older (both $P<.001$)

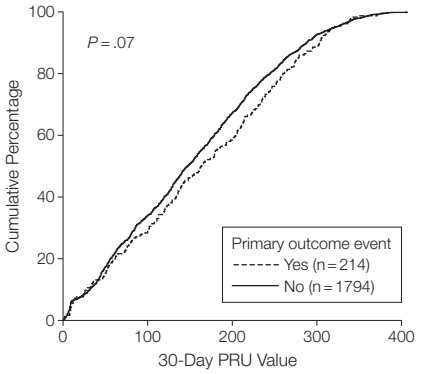
The proportion of participants from the overall population with high platelet reactivity cut points of more than 208 PRU and more than 230 PRU was high at baseline (range approximately, 45%-55%) and declined slightly with time in participants treated with clopidogrel but dropped to approximately 10% to 15% in prasugrel-treated group starting at the 30-day time point and remained consistent thereafter until the 30-month

Figure 2. Distribution and Median Serial $P2Y_{12}$ Reaction Unit Values During Treatment



The PRU values were measured at prespecified points through 30 months. A, Participants younger than 75 years and 60 kg or less were treated with prasugrel 10 mg/d or clopidogrel 75 mg/d. B, Participants younger than 75 years and weighed less than 60 kg were treated with prasugrel 5 mg/d or clopidogrel 75 mg/d. C, Participants 75 years or older were treated with prasugrel 5 mg/d or clopidogrel 75 mg/d. Horizontal bars represent median values; boxes, interquartile ranges around median values; and error bars, data points 1.5 or less × IQR. Outlier data points more than 1.5 × IQR are shown as dots above the error bars. *P* values compare the distribution of PRU values by treatment and time point.

Figure 3. Continuous Distribution Curves Showing $P2Y_{12}$ Reaction Unit (PRU) Values



Thirty-day values for 214 participants who experienced a primary composite end point event (cardiovascular death, myocardial infarction, or stroke) after the landmark time point of 30 days through 30 months compared with 1794 participants who did not experience an event. The *P* value compares the differences between groups across the continuous distributions.

measurement, when there were few participants with PRU values obtained (eFigure 2A and B, available at http://www.jama.com).

The cut point for high platelet reactivity based on ROC analysis showed limited discrimination but was determined to be PRU more than 178 (area under curve, 0.54; 95% CI, 0.50-0.58; sensitivity, 47%; specificity, 59%). Different patterns of high platelet reactivity status by treatment were demonstrated with the cut point of more than 178 PRU derived from this study, in that the proportion of participants with high platelet reactivity was higher in each treatment group at the specified time points than were the results with the other 2 cut points (eFigure 2C).

Clinical Outcomes and Platelet Reactivity

The Kaplan-Meier estimates of primary efficacy end point occurrence through 30 months were similar for participants included in the platelet function substudy analysis vs those who were not: 18.1% (340 total raw number of events) vs 19.3% (929 events; *P* = .48) and was not significantly different by prasugrel vs clopidogrel treatment among participants in the substudy analysis: 17.2% (160 events) vs 18.9% (180 events; *P* = .29). Likewise, estimates of all-cause death and all MI events through 30 months were similar based on inclusion in the substudy analysis: 11.0% (214 events) vs 11.9% (580 events; *P* = .74) for all-cause mortality and 10.2% (195 events) vs 11.5% (542 events) for all MI events (*P* = .45) and by treatment among participants in the substudy analysis: 10.5% (101 events) vs 11.5% (113 events) for all-cause mortality (*P* = .39) and 10.5% (96 events) vs 10.0% (99 events) for all MI events (*P* = .83).

Among participants in the substudy analysis, the continuous distribution curve for PRU values measured at 30 days by the occurrence of the primary efficacy end point after 30 days was not different for 214 participants with a primary end point event compared with 1794 participants without an event (*P* = .07; FIGURE 3). The 89 participants who experienced the primary efficacy end point; 26, all-cause mortality; and 88, MI before 30 days were thus excluded from the 30-day landmarked analyses.

Additionally, Kaplan-Meier event curves for the primary efficacy end point for participants with vs those without high platelet reactivity at 30 days determined by the predefined cut points of more than 208 and more than 230 PRUs diverged early after the 30-day landmark, appeared to separate more during long-term follow-up, and demonstrated a significant difference in the cumulative risk of events (FIGURE 4A and B). Similar findings were observed with the end point of all-cause death, but the difference in the cumulative risk of events was only significant by high platelet reactivity status for the cut point of more than 230 PRU (Figure 4C and D). In contrast, the event curves for all MI events diverged later during the follow-up period, but no significant difference in the cumulative risk of these events was demonstrated by high platelet reactivity status (Figure 4E and F).

When continuous PRU values (per 60-unit increase) were analyzed as a time-dependent covariate for the occurrence of the primary efficacy end point of cardiovascular death, MI, or stroke, there was no significant association after multivariable adjustment (adjusted hazard ratio [HR], 1.03; 95% CI, 0.96-1.11; *P* = .44; TABLE 2). Similar results were observed for all-cause death (adjusted HR, 0.99; 95% CI, 0.90-1.08; *P* = .79), and for all MI events (adjusted HR, 0.97; 95% CI, 0.88-1.07; *P* = .53). Similar results were seen when multiple imputation techniques were used for missing PRU values and when evaluating 30-day PRU values using a 30-day landmark analysis for ischemic outcomes.

When event occurrence was analyzed in relation to dichotomous high platelet reactivity determinations based on 30-day PRU values using the prespecified cut points of more than 230 and more than 208, as well as the cut point of more than 178 derived from this study, high platelet reactivity status was significantly associated with the end point analyzed in univariable fashion but was not found to be independently associated with the end points analyzed (Table 2).

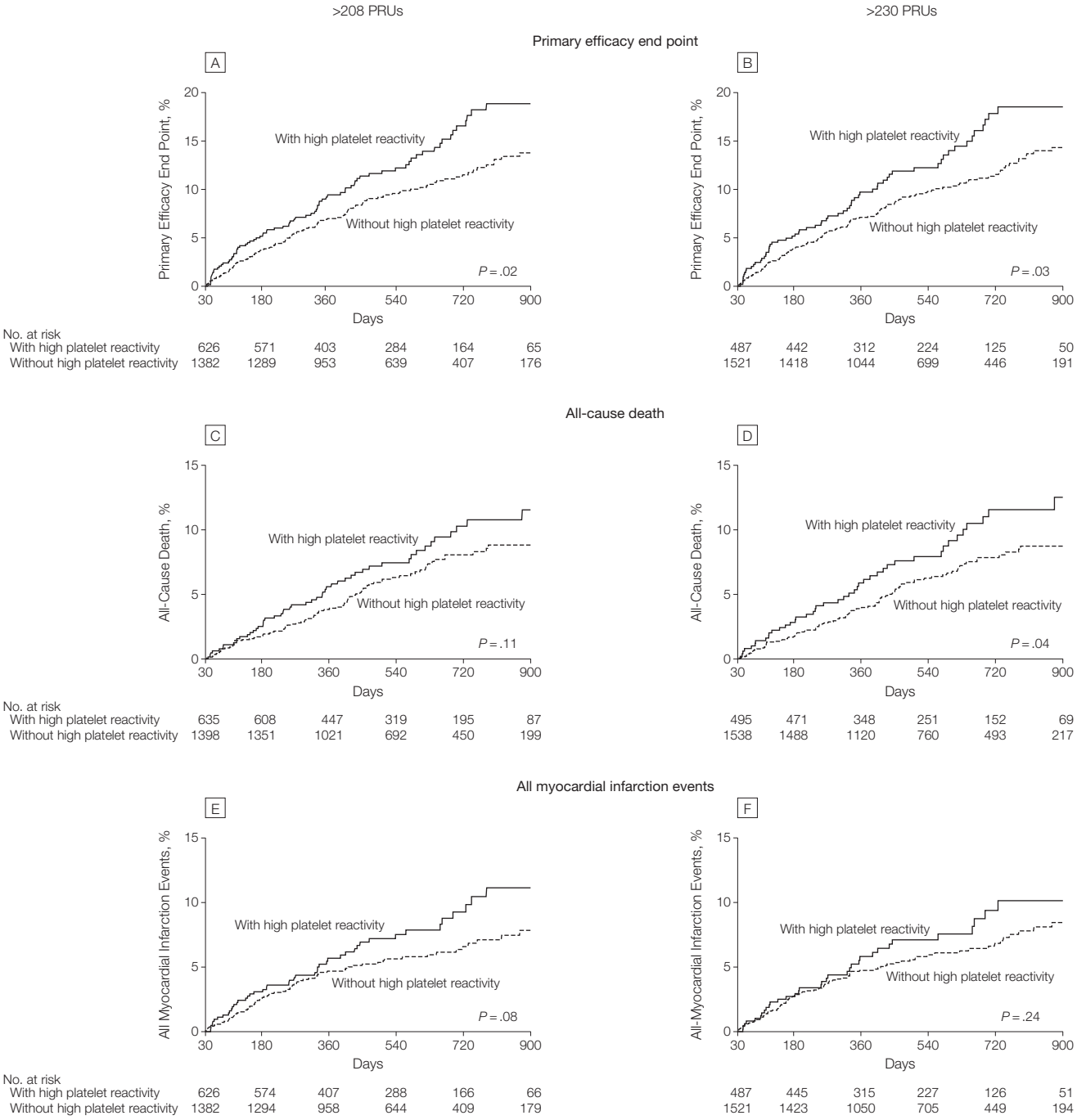
COMMENT

The TRILOGY ACS platelet function substudy provides several findings that may explain the overall trial results, which demonstrated no significant difference in ischemic outcomes through the first 12 months despite clinical observations of greater $P2Y_{12}$ receptor inhibition with prasugrel than with clopidogrel.[7] First, we demonstrated no significant independent association between both PRU values and high platelet reactivity cut points with ischemic event occurrence in patients with ACS without ST-elevation initially managed without revascularization. However, relatively few participants had platelet function measurements after 12 months, so the substudy results do not specifically inform the observation of a late, time-dependent separation of event curves in the main trial. Second, we have evaluated the longest longitudinal assessment of platelet reactivity for patients while treated with clopidogrel or prasugrel and demonstrated

a consistently greater pharmacodynamic response for prasugrel than for clopidogrel in all dosing groups.

Third, we have provided novel pharmacodynamic data on the 5-mg prasugrel dose in patients with ACS. This dose exhibited greater pharmacodynamic effects than did the 75-mg clopidogrel dose, but there was an attenu-

Figure 4. Kaplan-Meier Event Curves for the Primary Efficacy End Point, All-Cause Death, and All Myocardial Infarction Events



Starting at the 30-day landmark time point and continuing through 30 months are shown for patients with vs without high platelet reactivity from the 30-day platelet function measurement. High platelet reactivity was defined as more than 208 $P2Y_{12}$ reaction units (PRUs) and as more than 230 PRUs, as detailed in the "Methods" section. The *P* values shown on each panel compare the hazard between the 2 groups. The raw number of total events from 30 days through 30 months by those with or without high platelet reactivity for each panel are as follows: panel A: 133 vs 81; panel B: 87 vs 52; panel C: 78 vs 47; panel D: 150 vs 64; panel E: 95 vs 44; and panel F: 90 vs 35, respectively.

ated response compared with the 10-mg prasugrel dose.

We have demonstrated no significant association between PRU values and high platelet reactivity status with the occurrence of ischemic end points in an ACS population initially treated without revascularization. These findings were demonstrated within the context of observed stable, consistent differences in PRU measurements and less frequent high platelet reactivity status with extended-duration prasugrel vs clopidogrel treatment. Additionally, the continuous distribution curves for 30-day PRU values for participants with vs those without a subsequent primary efficacy end point were similar, and ROC analysis demonstrated relatively weak discrimination for the post hoc–derived high platelet reactivity status of more than 178 PRU in this population.

These findings collectively suggest that on-treatment PRU values are not strongly related to ischemic outcomes in patients with ACS that is managed medically, thus correlating with the primary results from the TRILOGY ACS trial, which demonstrated no difference by treatment assignment in the occurrence of the primary efficacy end point through the first 12 months. Thus, the mechanism of recurrent thrombotic event occurrence may differ in medically managed ACS patients compared with PCI-treated patients, for which it is strongly influenced by intensified $P2Y_{12}$ inhibition.

A single periprocedural measurement of high platelet reactivity in the setting of clopidogrel therapy for patients undergoing PCI has been associated with an increased risk of postprocedural MI and other ischemic outcomes, including stent thrombosis.[2,4-6] In the Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stents (ADAPT-DES) trial, the largest observational platelet function study conducted to date, close to 50% of 30-day post-PCI stent thrombosis was attributable to high platelet reactivity, defined as a PRU value of more than 208.[10] In addition, an increase of approximately 4-fold in risk of 30-day stent thrombosis was associated with a PRU measurement of more than 208.

Although high platelet reactivity while receiving treatment with clopidogrel is a well-established risk factor

Table 2. On-Treatment $P2Y_{12}$ Platelet Reactivity Unit Values and Risk of With Ischemic Events Through 30 Months

	Hazard Ratio (95% CI)			
	Unadjusted	*P* Value	Adjusted[a]	*P* Value
No imputation for missing values with PRU as a time-dependent covariate[b]				
CVD, MI, or stroke	1.09 (1.02-1.16)	.008	1.03 (0.96-1.11)	.44
All-cause death	1.09 (1.01-1.18)	.03	0.99 (0.90-1.08)	.79
All MI	1.02 (0.94-1.11)	.60	0.97 (0.88-1.07)	.53
Multiple imputation for missing values with PRU as time-dependent covariate[b]				
CVD, MI, or stroke	1.11 (1.04-1.19)	.002	1.05 (0.97-1.13)	.22
All-cause death	1.10 (1.01-1.21)	.03	1.02 (0.93-1.12)	.71
All MI	1.07 (0.98-1.17)	.12	1.01 (0.92-1.11)	.86
Multiple imputation for missing values with 30-d PRU values				
CVD, MI, or stroke	1.11 (1.03-1.20)	.007	1.04 (0.96-1.12)	.39
All-cause death	1.11 (1.01-1.22)	.03	1.01 (0.92-1.11)	.85
All MI	1.09 (0.98-1.21)	.10	1.02 (0.91-1.13)	.75
Multiple imputation for missing values with 30-d high platelet reactivity PRU cut point[c]				
>230				
CVD, MI, or stroke	1.43 (1.07-1.89)	.01	1.20 (0.90-1.61)	.21
All-cause death	1.46 (1.04-2.06)	.03	1.14 (0.80-1.62)	.48
All MI	1.27 (0.87-1.87)	.22	1.08 (0.73-1.61)	.69
>208				
CVD, MI, or stroke	1.43 (1.10-1.86)	.01	1.16 (0.89-1.52)	.28
All-cause death	1.38 (0.99-1.91)	.06	1.03 (0.74-1.44)	.84
All MI	1.37 (0.96-1.95)	.08	1.13 (0.79-1.62)	.50
>ROC-defined value of 178				
CVD, MI, or stroke	1.35 (1.05-1.73)	.02	1.13 (0.87-1.45)	.35
All-cause death	1.27 (0.92-1.75)	.15	0.99 (0.71-1.38)	.95
All MI	1.34 (0.96-1.86)	.09	1.13 (0.80-1.58)	.49

Abbreviations: CVD, cardiovascular death; MI, myocardial infarction; PRU, $P2Y_{12}$ reaction unit; ROC, receiver operating characteristic curve.

[a] Variables used in modeling for adjustment included those from the GRACE 6-month mortality risk score for patients with acute coronary syndromes (ACS) included age, chronic heart failure, prior MI, heart rate, creatinine levels, systolic blood pressure, ST-segment deviation, elevated cardiac enzymes, and no percutaneous coronary intervention for index ACS event and included variables specific to the TRILOGY trial: angiography before randomization, aspirin dose at randomization, baseline concomitant medications (β-blocker, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, statin, or proton-pump inhibitor), prior coronary artery bypass graft surgery, clopidogrel strata as previously defined,[7] diabetes, and smoking).[8]

[b] Evaluation of continuous PRU values (per 60-unit increase) as a time-dependent covariate with and without multiple imputation for PRU values expected to be measured for events occurring from 2 hours to 30 days (before the 30-day measurement) and for missing PRU values at the prespecified time measurements. PRU values assessed at 30 days were evaluated in the modeling process with a 30-day landmark analysis for events occurring after 30 days through 30 months with multiple imputation for missing PRU values at 30 days. High platelet reactivity PRU cutoff values at 30 days were introduced as dichotomous variables using the same landmarked modeling process.

[c] High platelet reactivity was measured while patients were receiving treatment.

for ischemic events among patients undergoing PCI, a large trial did not demonstrate that this risk was modifiable by increasing the clopidogrel maintenance dose to 150 mg (although with lower-than-expected event rates),[5] and a similar trial comparing prasugrel vs clopidogrel treatment among patients with stable coronary disease undergoing PCI was terminated early due to low event rates.[11] Thus, although high on-treatment PRU values for patients with stable coronary disease undergoing PCI who were treated with clopidogrel have been associated with worse outcomes in prior studies, randomized trials have shown that high platelet reactivity for PCI-treated patients receiving clopidogrel does not result in high event rates and does not discriminate a population of patients that has improved outcomes with adjustment of antiplatelet therapy.

A 5-mg dose of prasugrel was used in the TRILOGY ACS trial to reduce bleeding complications in the vulnerable groups of elderly (>75 years) patients and younger, low-body-weight patients (<60 kg). In pharmacodynamic studies of patients less than 60 kg and 75 years or older with stable coronary artery disease, close to 2 weeks of 5-mg prasugrel therapy was noninferior to 10-mg prasugrel used in younger, heavier patients, as determined by conventional platelet aggregometry.[12,13] The antiplatelet effects of the 5-mg prasugrel dose in these studies were greater than the effects with clopidogrel both among the elderly patients and younger patients with low body weight. These findings were confirmed in the much larger TRILOGY platelet function substudy using the VerifyNow $P2Y_{12}$ assay. A recent observational study showed that patients aged older than 75 years exhibited a reduced pharmacodynamic response to both clopidogrel and prasugrel; therefore, our findings should be considered within the context of differential response among elderly patients to both therapies evaluated in the TRILOGY ACS trial.[14] Thus, we have demonstrated reducing the prasugrel dose to 5 mg/d for subgroups shown to be at higher risk for bleeding is associated with an attenuated antiplatelet response compared with the 10-mg prasugrel dose in younger, heavier study participants, but the response was significantly greater than that observed with clopidogrel.[15]

A number of limitations to our analysis should be noted. PRU values were missing across all periods and multiple imputation techniques were used to account for any potential bias. Furthermore, the number of participants with PRU data after 12 months was relatively small, thus limiting the interpretation of PFS results with respect to the observed late divergence of event curves and the signal for a late reduction in multiple recurrent ischemic events in the overall trial.[7] Also, due to logistical issues, we were only able to collect a 2-hour PRU measurement after the start of study drug treatment that did not reflect subsequent steady-state PRU values that would typically be present only after 5 days of daily maintenance therapy in participants randomized to receive prasugrel therapy. Thus, we relied on PRU measurement taken at 30 days to examine the relationship between PRU and ischemic events occurring from 5 to 30 days and on the 2-hour PRU measurement for events occurring from randomization through 5 days. Finally, there was no mechanism to perform a formal sample size analysis for the substudy; accordingly, this study may have been relatively underpowered for assessing the relationship of on-treatment PRU values with the occurrence of ischemic end points.

In summary, we observed early and sustained differences in PRU values for medically managed ACS patients without ST-segment elevation treated with prasugrel vs clopidogrel, with relatively few study participants having platelet function measurements after 12 months. There were no significant differences in the composite of cardiovascular death, MI, or stroke through 30 months in patients treated with prasugrel vs clopidogrel and no significant independent association between platelet reactivity and the occurrence of ischemic outcomes.

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Online-Only Material: eFigures 1 and 2 and eTables 1 and 2 are available at http://www.jama.com.

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